

### **Amendments to the Claims**

This listing of claims will replace all prior version and listings of claims in the application:

#### **Listing of Claims:**

1. (Currently amended): A device for monitoring status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, comprising:
  - a. a first substrate having a first surface and an opposite second surface;
  - b. a second substrate supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein the body portion defines a first passage between the first side surface and the second side surface and an opening on the first surface of the second substrate and in fluid communication with the first passage;
  - c. sidewalls positioned above the first surface of the second substrate;
  - d. a third substrate having a first surface and an opposite second surface, wherein the third substrate, the sidewalls and the second substrate define a chamber, and wherein the chamber is in fluid communication with a second passage defined by portions of the sidewalls and the third substrate; [and]
  - e. at least one sensor positioned in the first passage proximate to the opening; wherein the cell is positioned in the chamber and the intracellular space of the cell is in fluid communication with the first passage through the opening of the second substrate; and
  - f. at least one seal element positioned on the second substrate and proximate to the opening for sealing the cell to the second substrate in operation.
2. The device of claim 1, wherein the membrane of the cell defines an opening through which the intracellular space of the cell is in fluid communication with the first passage through the opening of the second substrate.

3. The device of claim 2, further comprising a punching element positioned underneath the opening of the second substrate for making the opening defined by the membrane of the cell.

4. The device of claim 3, wherein the punching element comprises an electroporation device.

5. The device of claim 2, wherein when a first medium is introduced into the first passage, the intracellular space of the cell is in fluid communication with the first passage with the first medium, the sensor measures the response of the cell to the first medium.

6. The device of claim 2, wherein when a second medium is introduced into the chamber through the second passage, at least part of the membrane of the cell is in contact with the second medium in the chamber, the sensor measures the response of the cell to the second medium.

7. The device of claim 2, wherein when a first medium is introduced into the first passage and a second medium is introduced into the chamber through the second passage, respectively, the intracellular space of the cell is in fluid communication with the first passage with the first medium and at least part of the membrane of the cell is in contact with the second medium in the chamber, the sensor measures the responses of the cell to the first medium and the second medium.

8. The device of claim 1, further comprising a pair of first controls positioned inside the first passage for controlling the flow of a medium through the first passage.

9. The device of claim 1, further comprising a second control positioned inside the second passage for controlling the flow of a medium through the second passage.

10. The device of claim 1, wherein the first passage is in fluid communication with a reservoir of a medium.

11. The device of claim 1, wherein the second passage is in fluid communication with a reservoir of a medium.

12. (Currently amended): A device for monitoring status of a plurality of cells, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, comprising:

- a. a first substrate having a first surface and an opposite second surface;
- b. a second substrate supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein the body portion defines a first passage between the first side surface and the second side surface and a plurality of openings distributed on and over the first surface, each opening being in fluid communication with the first passage;
- c. a third substrate having a first surface and an opposite second surface and spaced apart from the second substrate thereby defining a space between the second surface of the third substrate and the first surface of the second substrate;
- d. a plurality of sidewalls positioned between the second substrate and the third substrate thereby partitioning the space between the second substrate and the third substrate into a plurality of chambers above the first surface of the second substrate such that only one of openings distributed on and over the first surface is located between the sidewalls of a corresponding chamber, wherein each chamber is in fluid communication with at least one neighboring chamber through a second passage defined by portions of the corresponding sidewalls and the third substrate; [[and]]
- e. a plurality of sensors positioned in the first passage, each sensor being proximate to a corresponding one of openings distributed on and over the first surface of the second substrate, wherein each cell is positioned in a corresponding one of the chambers and the intracellular space of each cell is in fluid communication with the first passage through the opening located between the sidewalls of a corresponding chamber; and

f. a plurality of seal elements positioned on the second substrate, each seal element is proximate to a corresponding one of the plurality of openings for sealing a corresponding cell to the second substrate in operation.

13. The device of claim 12, wherein the membrane of each cell defines an opening through which the intracellular space of the cell is in fluid communication with the first passage through the opening located between the sidewalls of a corresponding chamber.

14. The device of claim 13, further comprising a plurality of punching elements, each positioned underneath an opening located between the sidewalls of a corresponding chamber for making the opening defined by the membrane of a corresponding cell.

15. The device of claim 14, wherein each punching element comprises an electroporation device.

16. The device of claim 12, wherein when a first medium is introduced into some portion of the first passage, the intracellular space of a cell that is in a chamber corresponding to that portion of the first passage is in fluid communication with the first passage with the first medium, a corresponding sensor measures the response of the cell to the first medium.

17. The device of claim 12, wherein when a second medium is introduced into a chamber, at least part of the membrane of a corresponding cell in the chamber is in contact with the second medium, a corresponding sensor measures the response of the cell to the second medium.

18. The device of claim 12, wherein when a first medium is introduced into some portion of the first passage and a second medium is introduced into a chamber corresponding to that portion of the first passage, respectively, the intracellular space of a corresponding cell in the chamber is in fluid communication with the first passage with the first medium and at least part of the membrane of the corresponding cell is in contact with the second medium, a corresponding sensor measures the responses of the cell to the first medium and the second medium.

19. The device of claim 12, wherein the plurality of sensors are substantially the same.
20. The device of claim 12, wherein at least two of the plurality of sensors are different from each other.
21. The device of claim 12, further comprising a plurality of first controls positioned inside the first passage for controlling the flow of a medium through the first passage, wherein for each chamber, a corresponding pair of the first controls controls the flow of the medium through portions of the first passage under a corresponding chamber.
22. The device of claim 12, further comprising a plurality of second controls, each positioned inside a corresponding second passage for controlling the flow of a medium through that second passage.
23. The device of claim 22, wherein at least one chamber is in fluid communication with a reservoir of a medium through a second passage.
24. The device of claim 12, wherein the first passage is in fluid communication with a reservoir of a medium.
- 25 (Withdrawn): A method for monitoring the status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, comprising the steps of:
- a. confining the cell in a chamber;
  - b. making an opening in the membrane of the cell;
  - c. providing a first medium into the intracellular space of the cell through the opening in the membrane; and
  - d. measuring the response of the cell to the first medium.

26. (Withdrawn): The method of claim 25, further comprising the steps of:
- a. providing a second medium into the chamber such that at least part of the membrane of the cell is in contact with the second medium; and
  - b. measuring the response of the cell to the second medium.
27. (Withdrawn): The method of claim 26, wherein the first medium and the second medium are different.
28. (Withdrawn): The method of claim 26, wherein the first medium and the second medium are substantially the same.
29. (Withdrawn): The method of claim 26, wherein the second medium comprises an agent.
30. (Withdrawn): The method of claim 25, wherein the first medium comprises an agent.
31. (Withdrawn): A device for monitoring the status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, comprising:
- a. means for confining the cell in a chamber;
  - b. means for making an opening in the membrane of the cell;
  - c. means for providing a first medium into the intracellular space of the cell through the opening in the membrane; and
  - d. means for measuring the response of the cell to the first medium.
32. (Withdrawn): The device of claim 31, further comprising:
- a. means for providing a second medium into the chamber such that at least part of the membrane of the cell is in contact with the second medium; and
  - b. means for measuring the response of the cell to the second medium.

33. (Withdrawn): The device of claim 32, wherein the first medium and the second medium are different.

34. (Withdrawn): The device of claim 32, wherein the first medium and the second medium are substantially the same.

35. (Withdrawn): The device of claim 32, wherein the second medium comprises an agent.

36. (Withdrawn): The device of claim 31, wherein the first medium comprises an agent.

37. (Withdrawn): A method for monitoring the status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, comprising the steps of:

- a. confining the cell in a chamber;
- b. making an opening in the membrane of the cell;
- c. providing a first medium into the intracellular space of the cell through the opening in the membrane;
- d. providing a second medium into the chamber such that at least part of the membrane of the cell is in contact with the second medium; and
- e. measuring the response of the cell to the second medium.

38. (Withdrawn): The method of claim 37, further comprising the step of measuring the response of the cell to the first medium.

39. (Withdrawn): The method of claim 37, wherein the first medium and the second medium are different.

40. (Withdrawn): The method of claim 37, wherein the first medium and the second medium are substantially the same.

41. (Withdrawn): The method of claim 37, wherein the second medium comprises an agent.
42. (Withdrawn): The method of claim 37, wherein the first medium comprises an agent.
43. (Withdrawn): A device for monitoring the status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, comprising:
- a. means for confining the cell in a chamber;
  - b. means for making an opening in the membrane of the cell;
  - c. means for providing a first medium into the intracellular space of the cell through the opening in the membrane;
  - d. means for providing a second medium into the chamber such that at least part of the membrane of the cell is in contact with the second medium; and
  - e. means for measuring the response of the cell to the second medium.
44. (Withdrawn): The device of claim 43, further comprising means for measuring the response of the cell to the first medium.
45. (Withdrawn): The device of claim 43, wherein the first medium and the second medium are different.
46. (Withdrawn): The device of claim 43, wherein the first medium and the second medium are substantially the same.
47. (Withdrawn): The device of claim 43, wherein the first medium comprises an agent.
48. (Withdrawn): The device of claim 43, wherein the second medium comprises an agent.



49. (Withdrawn): A method for controlling the physiological status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein and controls its physiological status through an internal cellular control mechanism, comprising the step of:
- a. providing at least one medium to the cell such that at least part of the membrane of the cell is in contact with the medium to override the internal cellular control mechanism.
50. (Withdrawn): The method of claim 49, further comprising the steps of:
- a. confining the cell in a chamber; and
  - b. making an opening in the membrane of the cell.
51. (Withdrawn): The method of claim 50, wherein the providing step further comprises the steps of:
- a. supplying a first medium into the intracellular space of the cell through the opening in the membrane; and
  - b. supplying a second medium into the chamber such that at least part of the membrane of the cell is in contact with the second medium.
52. (Withdrawn): The method of claim 51, further comprising the steps of:
- a. measuring the response of the cell to the second medium; and
  - b. adjusting the composition of the second medium from the response to affect the overriding of the internal cellular control mechanism.
53. (Withdrawn): The method of claim 51, further comprising the steps of:
- a. measuring the response of the cell to the first medium; and
  - b. adjusting the composition of the first medium from the response to affect the overriding of the internal cellular control mechanism.
54. (Withdrawn): The method of claim 51, wherein the first medium and the second medium are different.

55. (Withdrawn): The method of claim 51, wherein the first medium and the second medium are substantially the same.
56. (Withdrawn): The method of claim 51, wherein the first medium comprises an agent.
57. (Withdrawn): The method of claim 51, wherein the second medium comprises an agent.
58. (Withdrawn): The method of claim 49, wherein the medium comprises an agent.
59. (Withdrawn): The method of claim 49, further comprising the step of:
- a. monitoring the concentration of at least one selected component of the medium;
- and
- b. adjusting the composition of the medium from the monitored concentration of at least one selected component of the medium to affect the overriding of the internal cellular control mechanism.
60. (Withdrawn): The method of claim 49, further comprising the steps of:
- a. measuring the response of the cell to the medium; and
  - b. adjusting the composition of the medium from the response to affect the overriding of the internal cellular control mechanism.
61. (Withdrawn): A device for controlling the physiological status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein and controls its physiological status through an internal cellular control mechanism, comprising:
- a. means for providing at least one medium to the cell such that at least part of the membrane of the cell is in contact with the medium to override the internal cellular control mechanism.

62. (Withdrawn): The device of claim 61, further comprising:
- a. means for confining the cell in a chamber; and b. means for making an opening in the membrane of the cell.
63. (Withdrawn): The device of claim 62, wherein the providing means further comprises:
- a. means for supplying a first medium into the intracellular space of the cell through the opening in the membrane; and
  - b. means for supplying a second medium into the chamber such that at least part of the membrane of the cell is in contact with the second medium.
64. (Withdrawn): The device of claim 63, further comprising:
- a. means for measuring the response of the cell to the second medium; and
  - b. means for adjusting the composition of the second medium from the response to affect the overriding of the internal cellular control mechanism.
65. (Withdrawn): The device of claim 63, further comprising:
- a. means for measuring the response of the cell to the first medium; and
  - b. means for adjusting the composition of the first medium from the response to affect the overriding of the internal cellular control mechanism.
66. (Withdrawn): The device of claim 63, wherein the first medium and the second medium are different.
67. (Withdrawn): The device of claim 63, wherein the first medium and the second medium are substantially the same.
68. (Withdrawn): The device of claim 63, wherein the first medium comprises an agent.

69. (Withdrawn): The device of claim 63, wherein the second medium comprises an agent.
70. (Withdrawn): The device of claim 61, wherein the medium comprises an agent.
71. (Withdrawn): The device of claim 61, further comprising:
- a. means for monitoring the concentration of at least one selected component of the medium; and
  - b. means for adjusting the composition of the medium from the monitored concentration of at least one selected component of the medium to affect the overriding of the internal cellular control mechanism.
72. (Withdrawn): The device of claim 61, further comprising:
- a. means for measuring the response of the cell to the medium; and
  - b. means for adjusting the composition of the medium from the response to affect the overriding of the internal cellular control mechanism.
73. (Withdrawn): A method for controlling the physiological status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein and controls its physiological status through an internal cellular control mechanism, comprising the steps of:
- a. providing at least one medium to the cell such that at least part of the membrane of the cell is in contact with the medium;
  - b. monitoring at least one selected component of the medium; and
  - c. adjusting the composition of the medium from the monitored concentration of at least one selected component of the medium to deliver or remove analytes to the intracellular space through the membrane to affect the internal cellular control mechanism.

74. (Withdrawn): A device for controlling the physiological status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein and controls its physiological status through an internal cellular control mechanism, comprising:

- a. means for providing at least one medium to the cell such that at least part of the membrane of the cell is in contact with the medium;
- b. means for monitoring at least one selected component of the medium; and
- c. means for adjusting the composition of the medium from the monitored concentration of at least one selected component of the medium to deliver or remove analytes to the intracellular space through the membrane to affect the internal cellular control mechanism.

75. (New): The device of claim 1, wherein the at least one seal element is formed and positioned to substantially encircle the opening.

76. (New): The device of claim 75, wherein the at least one seal element comprises an ohmic element.

77 (New): The device of claim 1, wherein the body portion of the second substrate further defines an intersection portion where the first passage and the opening on the first surface of the second substrate are in fluid communication, and wherein the intersection portion is at least partially formed as a cone shaped portion.

78. (New): The device of claim 12, wherein each seal element is formed and positioned to substantially encircle its corresponding opening.

79. (New): The device of claim 78, wherein each seal element comprises an ohmic element.

80. (New): The device of claim 12, wherein the plurality of seal elements are different or substantially same.

81 (New): The device of claim 12, wherein the body portion of the second substrate further defines a plurality of intersection portions where the first passage and the plurality of openings on the first surface of the second substrate are in fluid communication, respectively, and wherein each intersection portion is at least partially formed as a cone shaped portion.